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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/608,997	PROCKOP ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/18/07 has been entered.

Claims 1, 2, and 7 are amended.

Claims 16-17 are cancelled.

Claims 21 and 22 are newly presented.

Claims 1-7, 18, 21, and 22 are pending.

Claim Status, Cancelled Claims

In light of the cancellation of Claims 16 and 17, all objections and/or rejections of such claims are rendered moot, and thus, are withdrawn.

Claim Objections

In light of the amendments to Claim 17, the objection to such claim is withdrawn. Specifically, the predifferentiation step has been removed from Claim 17.

Specification

In light of the amendment, the previous objection to the specification is withdrawn.

To wit, the figures are now all properly described, due to the cancellation of Figure 7.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 1 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 22, which depends from Claim 1, requires the administration to be performed by direct injection. However, Claim 1 requires the injection to be into the brain of the patient, which is necessarily direct injection into the brain. Hence, these claims, despite a slight difference in wording, are substantial duplicates.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of the amendments, the previous rejections of Claims 1-7 and 17-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

To wit, Applicant now provides proper antecedent basis for "an astrocyte" in Claim 1, and also has cancelled Claim 17, removing all rejections previously of record.

Claims 1-7, 18, and 22 are newly rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those steps which are required for predifferentiation of stromal cells into astrocytes and when. At no point in the claims is any stromal cell predifferentiated into an astrocyte. Such leads to a further lack of clarity as to what the predifferentiation is relative to, i.e., a what point must the cell be predifferentiated to, to avoid being considered concurrent differentiation or post differentiation. Hence, these claims lack clarity.

Claim 18 requires the isolated stromal cells to be immunologically isolated. It is unclear whether is claiming that the cells are isolated from the immune system of the recipient upon administration, or whether they are isolated by immunological methods.

Claim Rejections - 35 USC § 112 - Enablement

Claims 1-7 and 17-18 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record, and as rewritten below for a

clear and concise record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-7, 18, and 21-22 are further rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Method steps critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Specifically, no step of predifferentiation is contained in the claims, while the method is drawn to providing stromal cells predifferentiated into astrocytes, while no step of predifferentiation is provided.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

It is noted that any particular factor may outweigh all factors, and even extraneous factors may overwhelm the other factors to make it such that undue experimentation must be found. Undue experimentation is not one of the amount of experimentation required *per se* but due to the fact that such experimentation would be required to reasonably predict the working embodiments encompassed by the claimed invention.

Breadth of the Claims

The claims encompass providing isolated syngeneic stromal cells which are predifferentiated into astrocytes to the brain of a human suffering from any disease, disorder or condition of the central nervous system. The method steps encompass isolating bone marrow from the syngeneic patient, isolating stromal cells from said bone marrow, and administering such stromal cells to the patient by injection into the brain of said patient in an amount of 10^5 to 10^{13} cells per 100 Kg patient.

It should be noted that these claims, drawn to "providing" are only encompassed by the confluence to encompass therapy of the disease, disorder, or condition, by such providing (e.g., SPECIFICATION, p. 5), and hence, the claims must be enabled for therapy of any disease, disorder, or condition of the central nervous system.

Claim 2 requires the donor to not be suffering from a disease, disorder, or condition of the central nervous system. Such claim necessarily requires that Claim 1 and the other dependent claims also encompass the donor to be suffering from the disease, disorder, or condition. Hence, as stated above, the Artisan would outweigh all the other factors with this fact to determine that such would not provide therapy, but would only add cells to the individual which would exacerbate the disease, disorder or condition. Moreover, nothing in the other factors has been found to outweigh this fact, and hence, it is undue experimentation to find those embodiments which would be efficacious in therapy when using such defective cells for therapy.

Claim 3 requires the donor to be human.

Claim 4 requires the disease, disorder or condition to be genetic disease, a tumor, trauma, or a stroke. Claims 5 and 6 further limit such to injury to the tissues/cells of the CNS or a brain tumor.

Claim 7 requires the administered stromal cells to remain or replicate in the CNS of the recipient.

Claim 18 requires the stromal cells to be isolated by immunological methods or are immunologically isolated from the recipient by some barrier.

Claim 21 requires the isolated stromal cells to be differentiated into astrocytes by co-culture *in vitro* with astrocytes, prior to administration to the patient.

The Nature of the Invention and State of the Prior Art

Applicant's invention is in the nature of somatic cell therapy for disorders, diseases, and conditions of the central nervous system in humans.

With regard to somatic cell therapy, a number of problems exist with regard to the transplanting of enough cells and an effect for a long enough period of time to effect treatment. To wit, Bartley, et al. (2003) Expert Opin. Biol. Ther., 3(4): 541-49 provides an overview for stem cell therapy for cerebral palsy (TITLE) which will suffice to delineate some of the problems with such therapies. Bartley only recognizes that two methods of administration appear to be feasible for treatment of cerebral palsy, those of intravenous or direct injection (p. 542, col. 1, paragraph 4), neither of which (meaning that specifically even direct injection), as will be shown below, is yet to be reasonably predictive of delivering enough cells to the site of action. In stating such, Bartley also recognizes that it is not reasonably predictable that any therapy can be effected with such cells injected into the vasculature, due to the permeability of the blood-brain barrier (Id.). Hence, Bartley is recognizing that administration, even when direct is not reasonably predictive of any particular treatment. Specifically, with palsy, as with many diseases of the central nervous systems, patients have differing effects with regard to amounts of grey or white matter (and specific cell types and ratios of cell types) being lost, and therefore, the type of cell used to effect such therapy must be able to reasonably predictably differentiate into each of the cell types in the correct proportions (p. 542, col. 1, paragraph 5), and, in fact, it is not even reasonably predictable which or whether both need to be replaced in any particular instance of the disorder (Id.). Therefore, even for any subset of diseases of the CNS, it is not reasonably predictable which cells to replace in the first place, much less whether marrow stromal cells, or even astrocytes, can do so for each cell type and in the correct proportions. Moreover, mere replacement of certain forms of cells may not effect any particular disease, as in palsy, where Bartley demonstrates that it is not reasonably predictable that replacement of myelin, without

replacement of the axons themselves, would facilitate any functional improvement (p. 542, col. 2, paragraph 2).

Bartley also indicates that the choice of cell type, stage of differentiation, and derivation a critical issue, indicating the specific stem cell may not be efficacious for any particular form of palsy, much less any disorder of the central nervous system (Id., paragraph 3). With regard to bone marrow stromal cells, Bartley recognizes that crude bone marrow can generate neural progenitor cells in culture and individuals at autopsy who had received bone marrow transplants have been shown to comprise neurons arising from the transplant (p. 543, col. 2, paragraph 4). However, such evidence does not enable Applicant's invention, because it is post-filing evidence, citing articles that are post-filing evidence, and these articles teach *in vitro* differentiation, and the patients had whole bone marrow transplants, not stromal cell implants. Still further, the simple presence of structure (the cells being present) does not reasonably predict functional replacement to affect therapy (e.g., Swallow, et al. (1999) Restorative Neurology and Neuroscience, 15(4): 297-303 demonstrates that although structure may form, the functional connections required may not be formed by the cells, even in the case of native cells of the CNS). Hence, simply adding a bone marrow stromal cell, even if it differentiates into a astrocyte and further into the various cell types required to treat the disease, even if in the proportions required, the Artisan would not reasonably predict that the required functional connections are formed such that therapy would be affected in any particular disorder.

Still further, in some disorders the in many forms of disease/disorder/condition, the problem is not reasonably predicted to be solved by adding more cells in any form, but would require replacement of the existing cells to solve the problem. To wit, Keller, et al. (2000)

Neuroscience, 98(1): 149-56 demonstrates that proteosome activity causes degeneration of aging spinal cord (whole article). It is unclear how other cells will cause these cells to repair their proteosome activity. Hence, again, in any specific form of disease, disorder, or condition, it is not reasonably predictable that therapy could be affected.

Bartley also provides numerous lines of evidence to indicate that marrow stromal cells can differentiate into various tissues and that such **may** be able to occur *in vivo* (p. 544, col. 1), but also there exists conflicting data (Id., paragraph 2), and hence, the Artisan would still not reasonably predict it to be efficacious in any specific embodiment even if it properly differentiated into the needed tissues and form the required connections with the CNS required. Further, Bartley questions the use of undifferentiated cells, and indicates that it is not reasonably predictable yet, requiring further exaperimentation, to determine the state of differentiation which should be applied in any particular treatment of any particular disease, disorder or condition (p. 544, last paragraph). Furthermore, it is noted that even when these cell differentiate in some fashion, it is not clear whether such is the source of the therapeutic effect, or whether recovery is mediated by some other substance elaborated by the implanted cells (p. 545, col. 1, paragraph 2), and therefore, even if the cells differentiate they may actually not cause any therapeutic effect at all in any particular embodiment. Moreover, other results indicate that improvements in function may not be linked to the implantation of the cells themselves (Id., col. 2, paragraph 1), making the results suspect for any therapy associated with stromal cell therapy to the brain. Also, Bartley, even when a finding seems positive, indicates the need for further confirmation of the information before the data can be fully accepted (Id.).

In conclusion, Bartley indicates that while the data is encouraging, extensive experimentation is still required before human treatment will be feasible (p. 545, col. 2, paragraph 2; p. 546, col. 1). Clearly, Bartley is indicating that somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans at this point, which is even after Applicant's filing date.

Hence, from reviewing Bartley, the Artisan would only be able to make one conclusion: somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans. This is because it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that the cells, even if they form in the correct amounts will form the correct functional connections with the nervous system; it is not reasonably predictable that the replaced cells, even if forming the correct functional connections would correct an already present problem; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; and it is not reasonably predictable that if the transplanted cells have the same disease, disorder or condition that therapy would be affected.

Savitz, et al. (2003) J. Cardiovasc. Nurs., 18(1): 57-61 further demonstrates that these bone marrow stromal cells are not yet reasonably predicted to treat human CNS diseases in another context: that of stroke recovery (TITLE). While focusing on neural progenitors and fetal stem cells, Savitz discusses the possible use of stromal cells as another "potential" graft source for the treatment of strokes (p. 59). In it, Savits comments on Li, demonstrating "intriguing therapeutic possibilities" through these preliminary results (p. 59, col. 2, paragraph 2). However, Savitz also concludes that "much work lies ahead" because it remains largely unknown to what extent the different stem or progenitor cells differentiate into neurons or other brain cells, echoing the seniments expressed in Bartley (p. 60, col. 1). Furthermore, it is unknown if any particular stem cell would yield the correct percentage of progeny needed to reconstruct specific brain regions, what factors within the brain will support or the viability of such grafts, and will they integrate safely (p. 60, paragraph bridging columns). Hence, as Savitz concludes "Answering these and many other questions will require **extensive investigation** in order to yield useful data from which to draw practical information" (Last sentence, emphasis added).

Therefore, Savitz, in discussing a different disease, stroke, also concludes that much more experimentation is needed to elucidate the various problems of such somatic cell therapy for brain disorders. Such is also clearly linked to the type of stem cell, whether it will differentiate properly, and whether enough cells will be present and have enough of an effect for a long enough period of time to effect treatment, and/or whether the cells will actually integrate and replace the dysfunctional tissues of the brain.

Moreover, Horn, et al. (2004) Molec. Ther., 10(3): 417-431, demonstrates that the small animal studies, in which most experiments have been performed to date (e.g., rodents), even if

they are efficacious of treating a particular disease, are not reasonably predictive of treatment in humans. Horn discusses the potential of hematopoietic stem cells, stating that the use of such in stem cell therapy has great promise for the future, but does not recognize any currently reasonably predictable treatment for such stem cells (p. 417, paragraph bridging). (It should be noted that while the Examiner acknowledges that the reference is drawn specifically to treating central nervous system disorders, the issues to be raised (below) extend to all forms of treatment by stem cell gene transfer, and not just the treatment of the hematopoeitic system or ex vivo gene therapy with such cells; and if Applicant wishes to take issue with any of these art-recognized problems, the Examiner requests a scientific explanation of why such issue is not pertinent to Applicant's claimed therapy.) Horn first demonstrates that in initial results, it was shown that mouse hematopoeitic stem cells could be genetically modified with a degree of efficiency predicted to be therapeutic for many human diseases; however, in later experiments it became apparent that such therapy did not work in humans (p. 417, col. 2, paragraph 2). Hence, it is not reasonably predictable that mouse systems of gene therapy in stem cells is not predictable of therapy in humans. Next, Horn discusses the fact that large animal models may be better models for therapy in humans, but that such experiments are very labor intensive (p. 418). Also, similar to Bartley's conclusions, the source and differentiation state of the stem cell is critical and is not yet predictive of treatment of any particular disease (pp. 424-425, paragraph bridging). Further, while still not being considered reasonably predictable at this point, Horn emphasizes that large animals models are needed to be examined to determine therapy, and that the small animals used, as in Applicant's experiments (below), are definitely not reasonably predictive of therapy in humans (pp. 426-427), and that such is due to, for example, the different endocrine signals and

distinct stem cell pathways which larger animals have, which are different between the larger primates and the smaller ones (p 425, col. 1).

Hence, from Horn we see that the use of stem cells, even when genetically modified to further more closely resemble the tissues required to be replaced, that therapy is generally not predicted when it is efficacious in animals. Moreover, while it may be argued that majority of Horn is drawn to ex vivo gene therapy, Horn is still recognizing the same problems with regard to the models, i.e., that the replacement therapy may be effective in a rodent, but not in a human. To wit, in every case, the cells are required to provide the functional connections with the system to replace the malfunctioning cells, and as such, whether or not it is provided by administration of cells alone, or a cell that secretes a protein, such functional connection, when formed in a rodent model does not reasonably predict treatment of humans.

Lastly, with regard to immunologically isolated, if such cells are immunologically isolated, then the factors and such that the cells produce cannot reach the adjacent cells, and therefore no therapy could reasonably be effected in any particular disease, particularly if the disease requires the cells to differentitate into cells of the central nervous system as those cells would be required to become part of the CNS, and not just exist nearby. To put this in perspective, if you placed brain tissue within someone's brain, it is not predictable that the brain tissue would be part of the brain, but simply garbage inside the brain. The cells would need to integrate, and immunological isolation would inhibit such integration.

In reviewing the above references, it is clear that the artisan would find any particular stem cell therapy in humans not reasonably predictable because: it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and

direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that even if structural recovery is obtained that such will equate to functional recovery; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose any therapy of any central nervous system disorder in a human, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and

its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Direction and Guidance Provided By Applicant

Applicant's specification broadly discusses the treatment of neurological damage in many diseases and the potential for the use of stromal cells (pp. 1-5), a summary of the invention broadly tracking the claims (pp. 5-7), definitions (pp. 9-14), broad disclosure of stromal cells, where they are isolated from, and predictions of ability to treat disease (pp. 14-21), further broad discussion of such cells with transgenes (pp. 21-25), culturing conditions (pp. 25-26), and administration methods and more culturing conditions (pp. 26-33).

However, such broad description does not constitute the specific direction and guidance the Artisan would require to reasonably predict whether, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in*

vivo in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

The Existence of Working Examples

Example 1 demonstrates that stromal cells may contribute to connective tissue differentiation. Example 2 demonstrates the conditions for culture and isolation of stromal cells. Example 4 demonstrates long-term expression of genes in such cells. Example 5 demonstrates expression of such genes in subcutaneous diffusion chambers. Example 7 demonstrates that after direct administration of the stromal cells into rat brains, such cells may be found in the brains of rats for many weeks after administration, and migrate into various portions of the brain. Example 8 demonstrates that in the presence of astrocytes, the stromal cells exhibit a single marker of early astrocyte differentiation: glial fibrillary acidic protein.

Such examples however fall far short of the knowledge produced in the art, as described by the two articles provided above. They do not reasonably predict any therapy in humans for reasons given in the art and nature of the invention: mouse models and xenotransplantation in small animals is not reasonably predictive of any therapy in humans, even when cells produce physiologically relevant levels of genes (above). Moreover, they do nothing to overcome the lack of reasonable predictability it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that

mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

Undue Experimentation

Due to the reasons given in the last paragraph, the Artisan would have to perform undue experimentation to treat any particular disease, through any particular form of administration of such stromal cells, at any particular level of differentiation, with or without any particular transgene and promoter and other regulatory elements, with or without immunological isolation, to treat any particular instance of any disorder/disease/condition, due to the lack of reasonable predictability.

Such experimentation is considered extensive and undue.

Conclusion

Applicant's claimed invention is considered non-enabled for its whole scope due to the requirement for undue experimentation to find any particular working embodiment.

Response to Argument - Enablement

Applicant's arguments of 10/15/07 have been fully considered but are not found persuasive.

Applicant argues that given the direction provided and Example 7, demonstrating transplantation of cells and subsequent persistence for 5-72 days, the embodiments are enabled (pp. 6-7).

Such is not persuasive. Simple presence of cells is not predictive of therapy for the reasons given above. Moreover, rodent models are not predictive of therapy in humans.

Applicant argues that rodent models are reasonably predictive, citing the Ungerstedt rat model of Parkinson's disease (p. 7, paragraph 3).

Such is not persuasive. A single model, with a specific demonstrated efficacious effect, that of replacement drug therapy does not equate to enabling any therapy in any rat, particularly when the model does not even have a disease which is corrected.

Applicant submits that Horn is not relevant (p. 7, last paragraph).

Such is not persuasive. Horn, as shown above, demonstrates that the rodent models are not reasonably predictive of therapy in humans, and that such appears to be due to distinct functional integration of the applied therapy.

Applicant argues that Horn's stem cells have less stemness than the presently applied bone marrow stromal cells, and hence, Horn is not properly applied (p. 8, paragraph 1).

Such is not persuasive. The "stemness" is not at issue in Horn, but instead many other issues. Obviously, the stemness of Horn's cells was considered sufficient for the therapies to be treated. Hence, for the therapies encompassed, the stemness appears to not be an issue.

Applicant argues that Savits, in stating that preclinical animal data has set the stage for limited clinical trials with autologous BMSCs, and as such, the methods are enabled (p. 8, paragraph 2).

Such is not persuasive. Savits' limited clinical trials are known to be only trials for safety, and are not required to meet the level of enablement, but only that of utility. Applicant does not face a utility rejection.

Applicant argues that Bartley is not relevant as it only discusses cerebral palsy, and describes numerous methods that are successful, and hence, the claims are enabled for their breadth (p. 8, last paragraph-p. 9, paragraph 1).

Such is not persuasive. Bartley discusses an example set of disorders, the palsys. They do not work. Still further, with regard to these plethora of successful treatments, the Examiner fails to find any successful treatment, and it would appear that Applicant has misread Bartley. However, broad argument does not supplant for explicit demonstration of the lack of logic or incorrect facts that would alter the Examiner's analysis. Still further, the other references expound similar problems, and the Artisan would not understand these problems of Bartley not to be important to any particular disorder. Lastly, the Applicant appears to confuse the presence of differentiated cells to mean therapy, however, no therapy is provided in Bartley that would make Applicant's methods reasonably predictive of therapeutic effects in humans, and also especially given the breadth of disorders and the lack of understanding to reasonably predict success of any particular embodiment, of which all embodiments claimed must be enabled for therapy.

Applicant cites Li, Zhao, and Chen references in Bartley, to argue that therapy is found, and that even Bartley states that human treatment in these conditions may be beneficial, to argue that the methods are enabled (pp. 9-10, paragraph bridging).

Such is not persuasive. Li, Zhao, and Chen are essentially the same therapy: induced infarction in rodents. Applicant has not limited their claims to such. Still further, the Art cited is post-filing evidence. Still further, Bartley's statement that it may be beneficial is only one of utility, not enablement. Still further, the confluence of Bartley still demonstrates that the Artisan does not find the methods enabled for therapy. Still further, it is clear from the Art cited that the rodent models are not yet reasonably predictive of therapy in humans.

Applicant argues that optimization of doses is not undue experimentation as the Artisan could determine such (p. 10, paragraph 3).

Such is not persuasive. No dosage in any case is known to be therapeutic for any particular embodiment. Hence, these dosages are undue experimentation as they are required to tried to find if any of them would produce a therapeutic effect.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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